Chemical pollutants

toxicology, effects

Prof David Vernez | Chef de département

unisanté
Centre universitaire de médecine générale et santé publique · Lausanne

Département Santé Travail - Environnement
Rte de la Corniche 2
CH-1066 Epalinges-Lausanne
Tél. +41 21 314 74 51
www.unisante.ch

Presentation plan

What is toxicity?

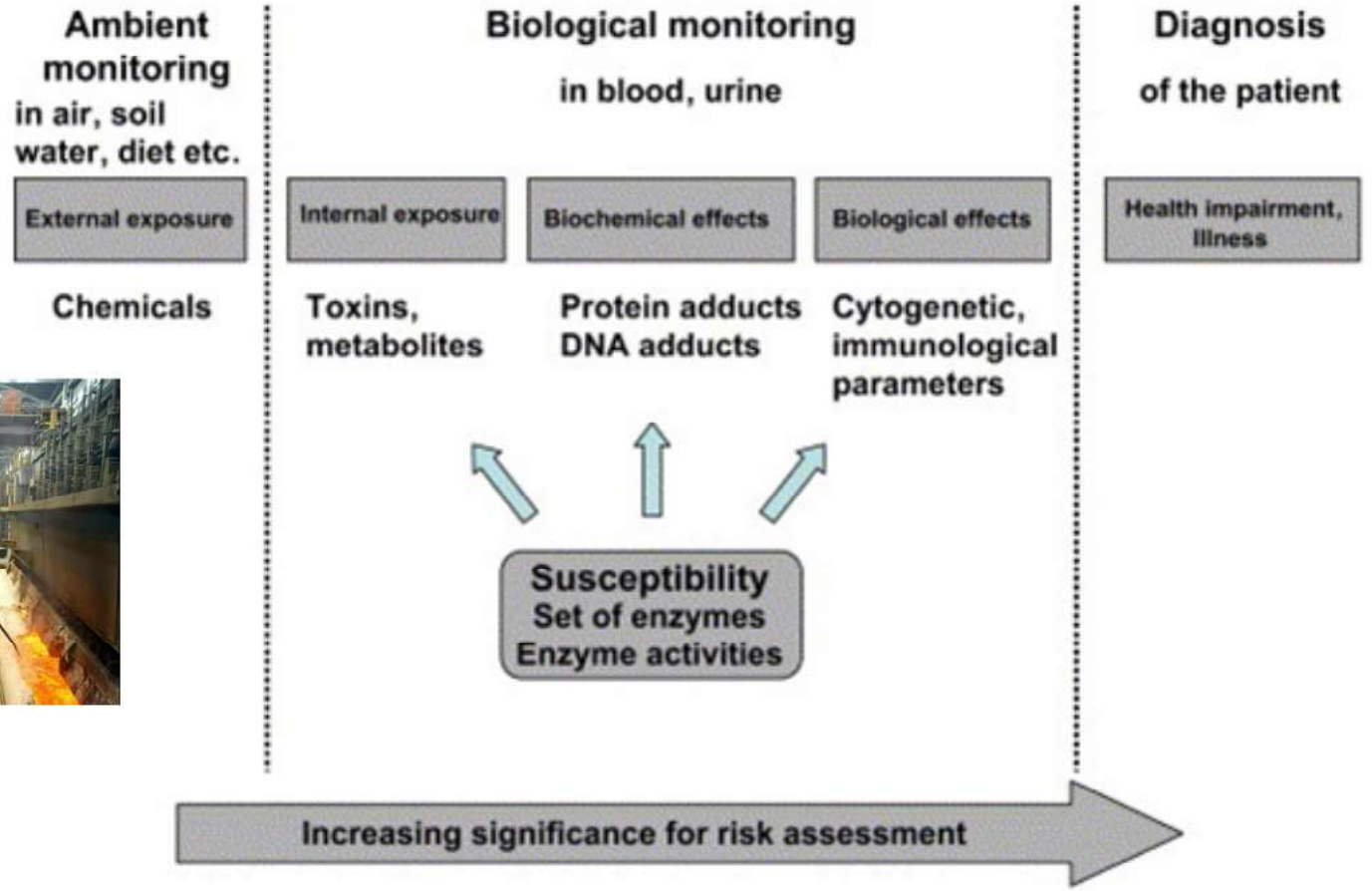
Toxicological evaluation

ADME

Biological monitoring

Example: aluminum smelter worker

From the source to the disease

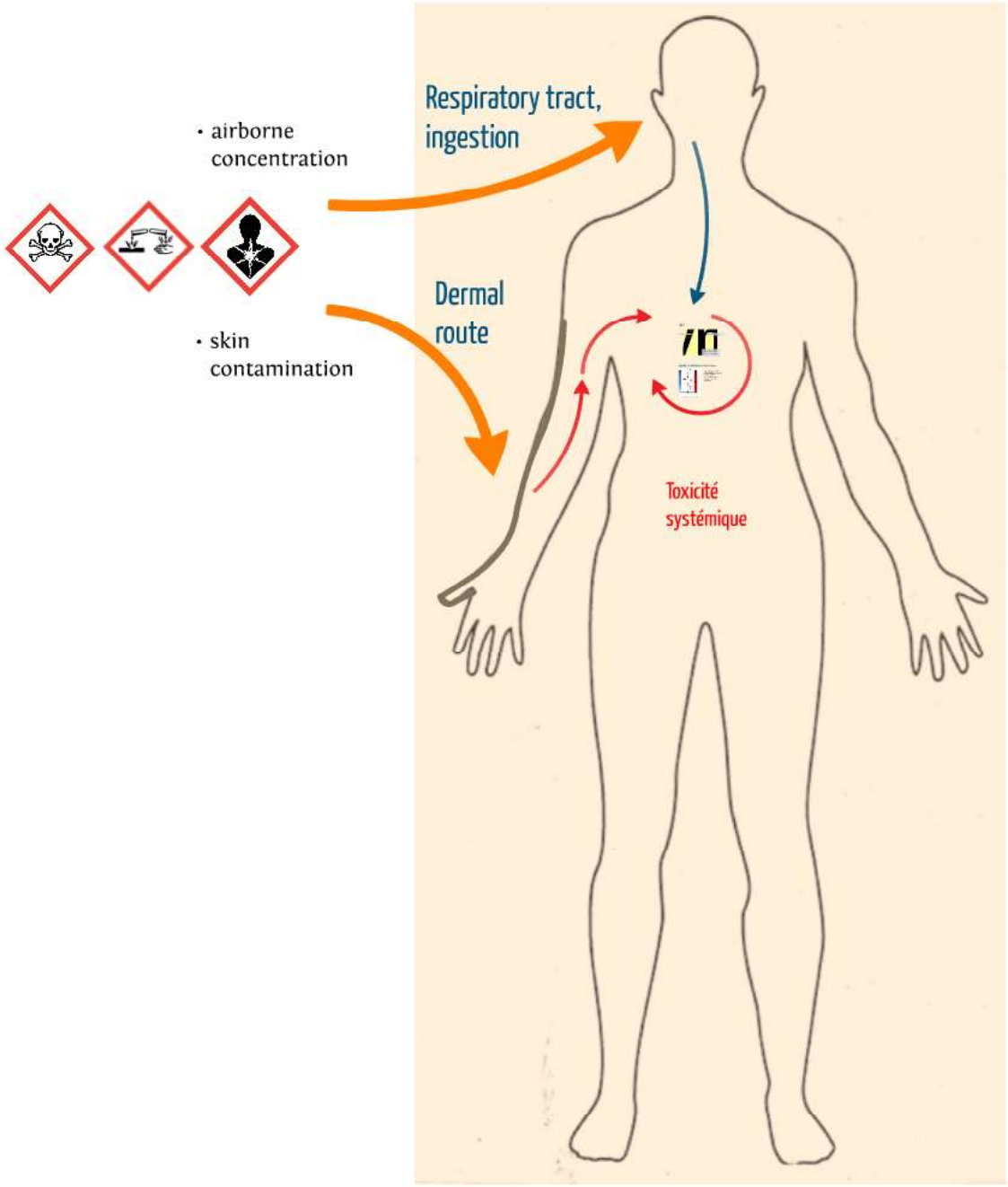


Scheme of ambient and biological monitoring (modified acc. DFG, 2002; Angerer and Gündel, 1996)

Toxicity

What is it ?

- An observable or measurable physiological alteration, reversible or not
- Observable in different species
- Against which the body's protective mechanisms are insufficient
- Which implies a dimension of quantity or dose
- The toxicity of a chemical substance depends on its degree of exposure, absorption, distribution, metabolism and excretion (ADME)



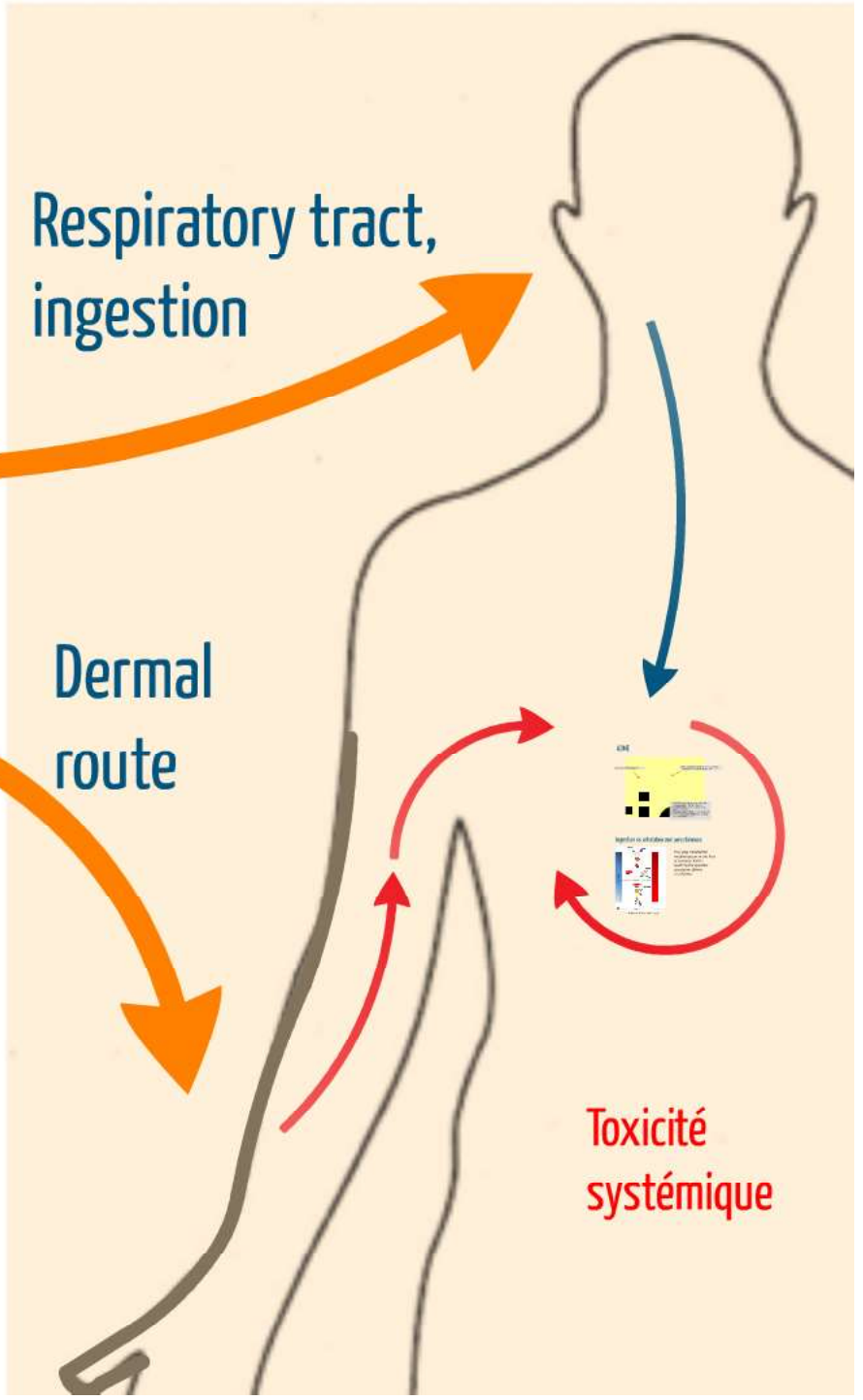
Toxicokinetics

Evaluation

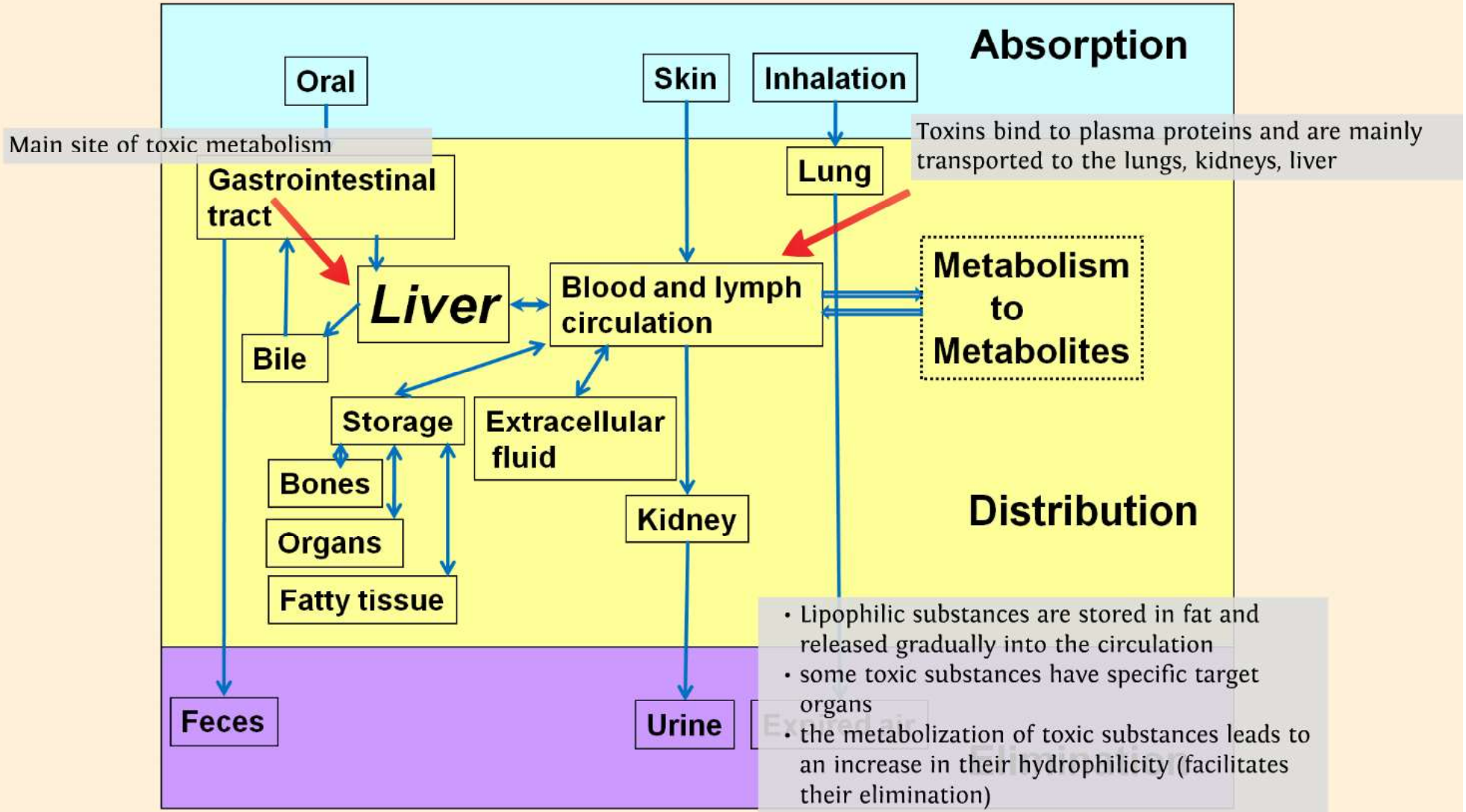
Reference values

- airborne concentration

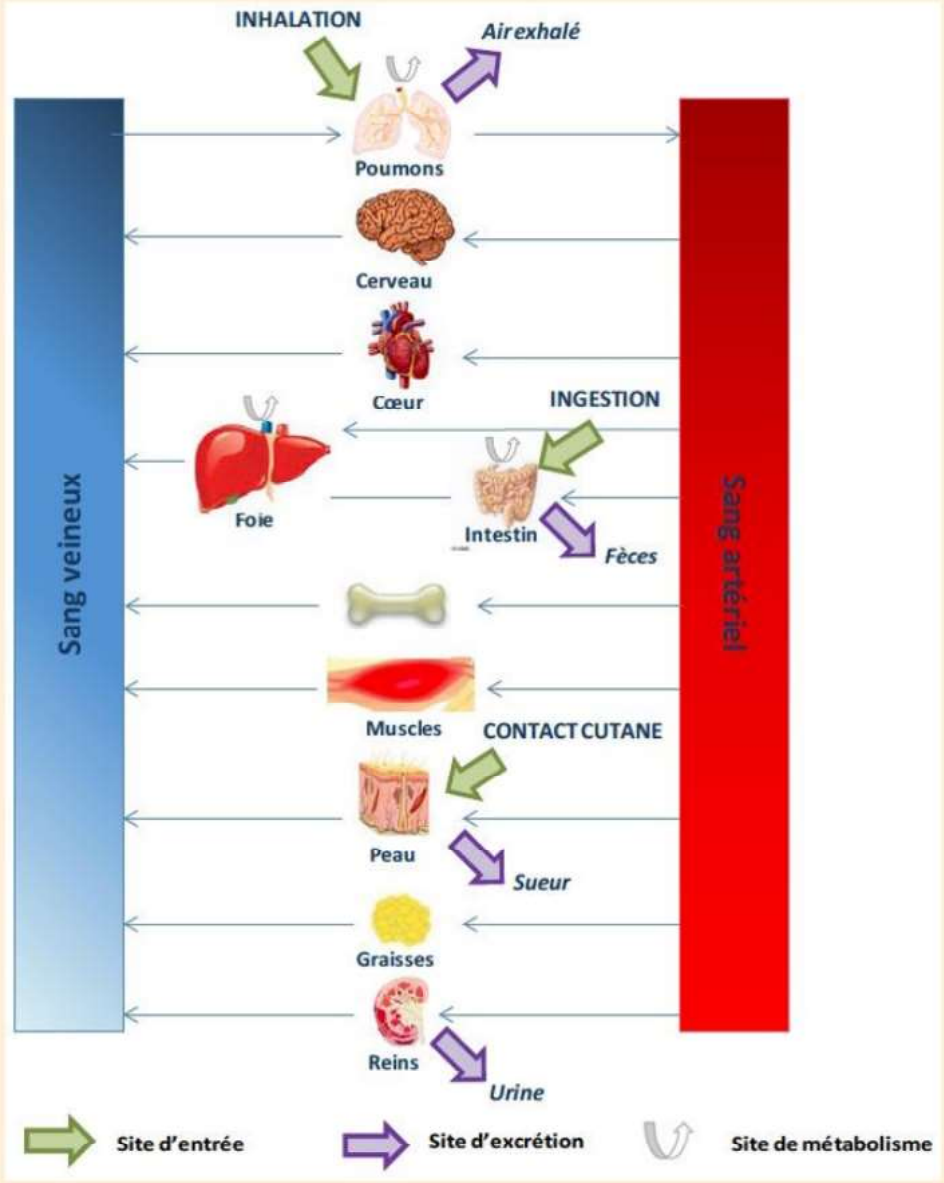
- skin contamination



ADME


Absorption
Oral
Skin
Inhalation
Main site of toxic metabolism
Toxins bind to plasma proteins and are mainly transported to the lungs, kidneys, liver
Gastrointestinal tract
Lung
Liver
Blood and lymph circulation
Metabolism to Metabolites
Bile
Storage
Extracellular fluid
Bones
Organs
Fatty tissue
Kidney
Distribution
Feces
Urine
• Lipophilic substances are stored in fat and released gradually into the circulation
• some toxic substances have specific target organs
• the metabolization of toxic substances leads to an increase in their hydrophilicity (facilitates their elimination)

Ingestion vs. inhalation and percutaneous



First-pass metabolism: metabolization in the liver or intestine before reaching the systemic circulation (blood circulation)

Modéliser & simuler – Tome 2 (2014)

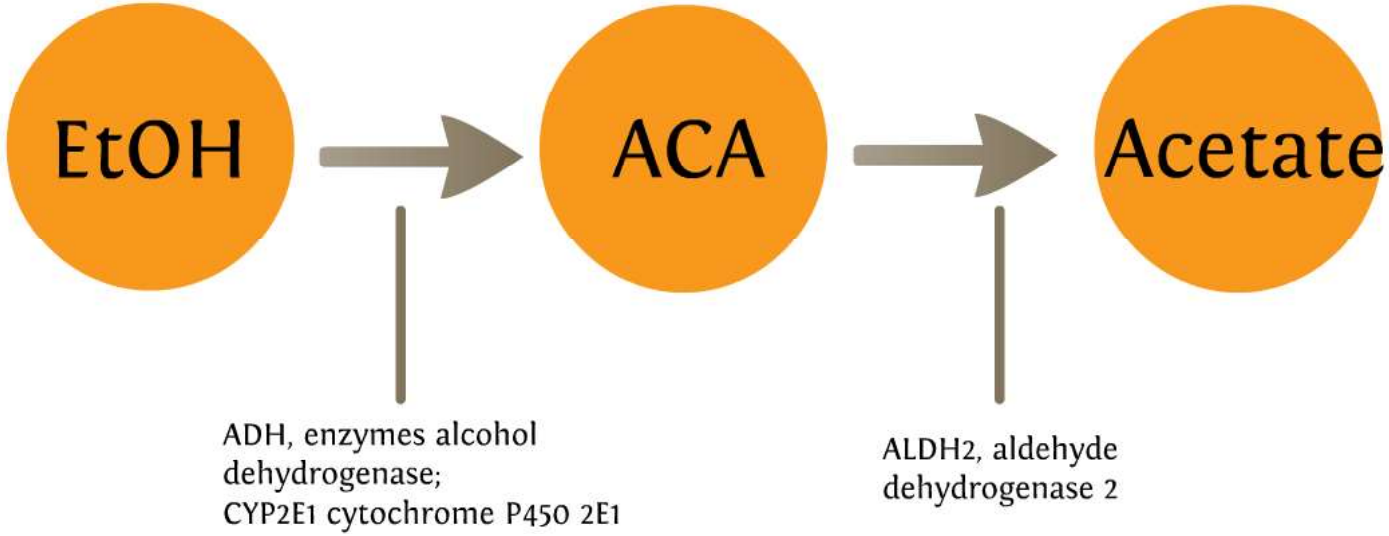
Elimination - zero order kinetics

Properties

- The rate of elimination is independent of the concentration of the toxic substance

Example: Ethanol

- Main metabolism

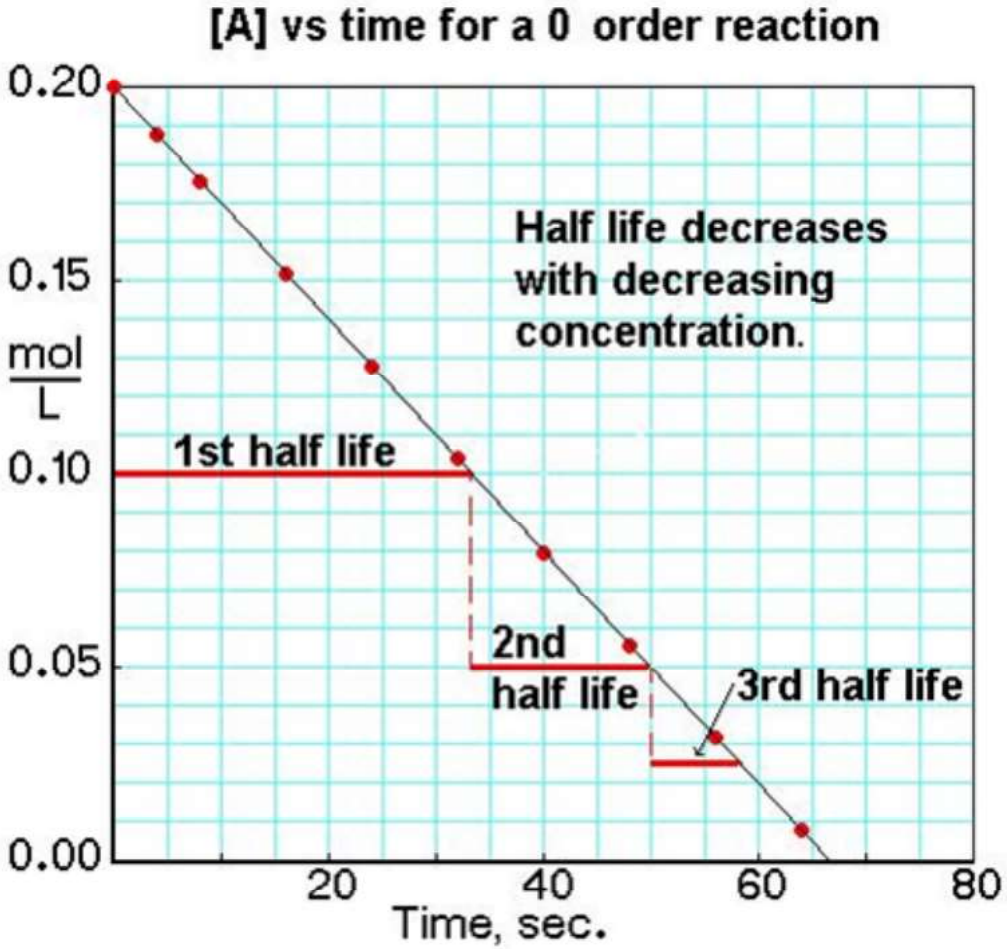


Elimination - zero order kinetics

Ethanol elimination

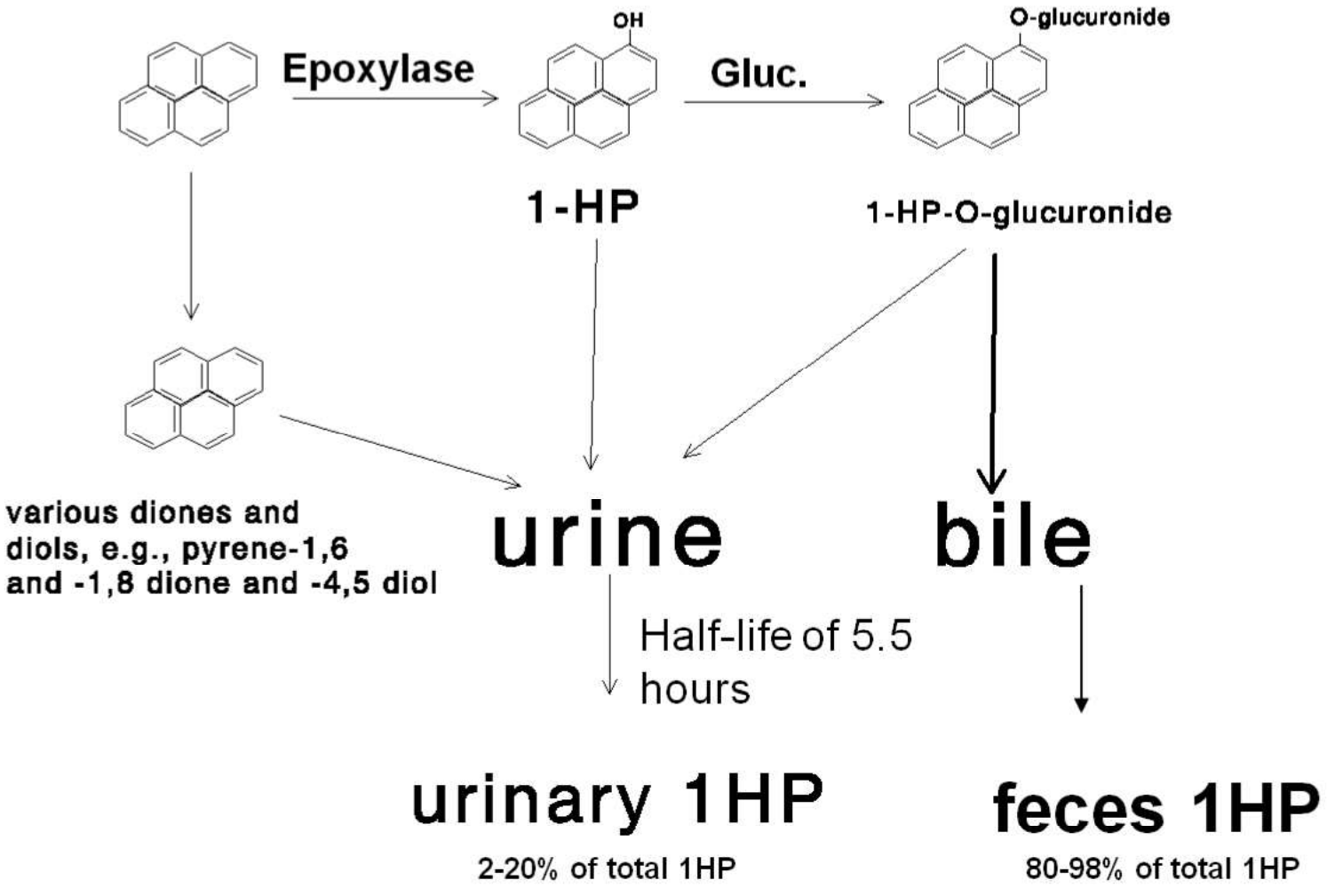
- independent of the concentration of the toxicant
- constant speed

$$t1/2 = [A0] / 2k$$



Elimination - first order kinetics

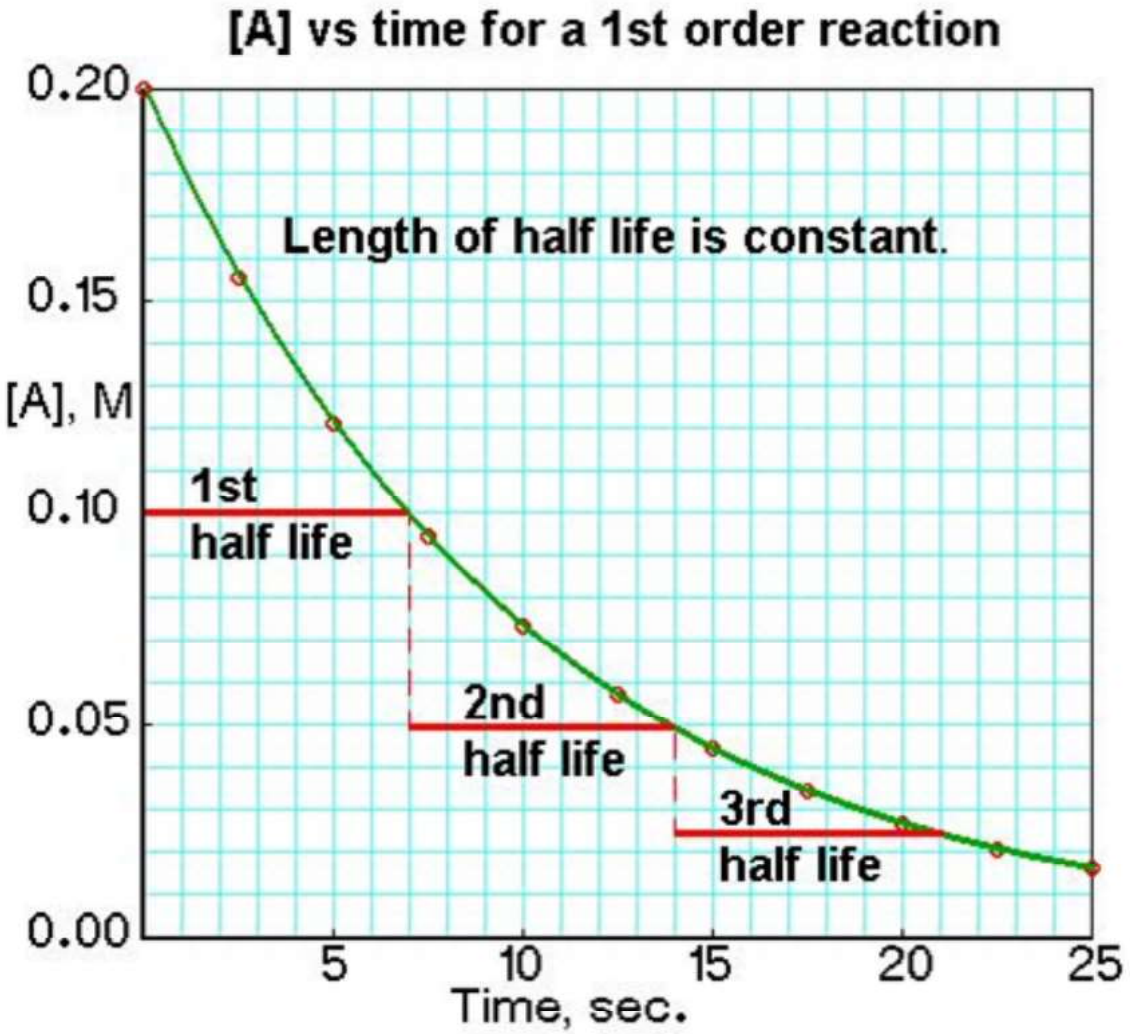
Example of exposure to PAHS in foundries



Elimination - first order kinetics

- elimination proportional to the concentration of the toxicant
- a constant proportion of the toxicant is eliminated per unit of time

$$t_{1/2} = \ln 2/k$$



Elimination kinetics

Zero order elimination

$A \rightarrow$ products

rate = k [mol L^{-1} s^{-1}]

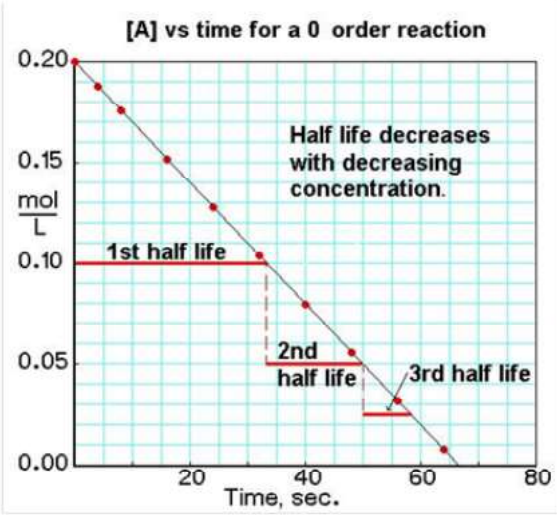
$[A] = [A_o] - kt$

$t_{½} = [A_o] / 2k$

- Constant elimination
- Independent of amount of chemical in the body

Ex. Ethanol

No-model



First order elimination

$A \rightarrow$ products

rate = $k[A]$ [s^{-1}]

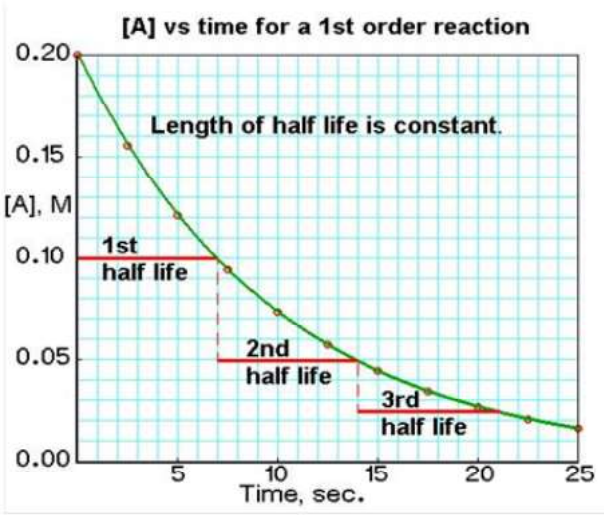
$[A] = [A_o] e^{-kt}$

$t_{½} = 0.693 / k$

- Constant proportion of the agent is eliminated per unit time
- Logarithmic process

Ex. Most chemicals

One-compartment toxicological model



Second order elimination

$2A \rightarrow$ or $A + B \rightarrow$ products*

rate = $k[A]^2$ [L mol^{-1} s^{-1}]

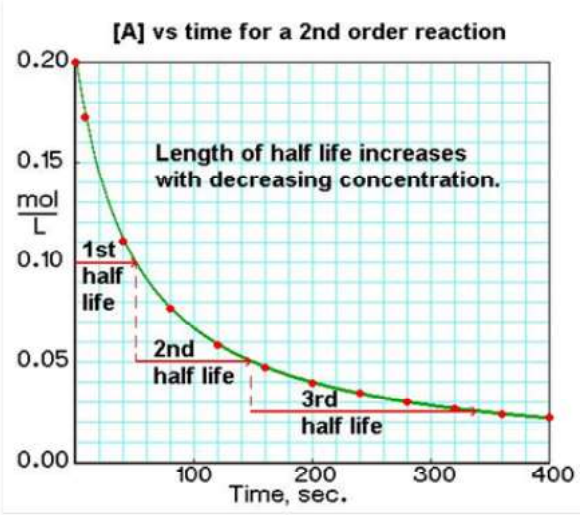
$1/[A] = 1/[A_o] + kt$

$t_{½} = 1 / k [A_o]$

- Chemical concentrations in tissues takes time to reach equilibrium with plasma

Ex. Persistent chemicals

Multi-compartment toxicological model



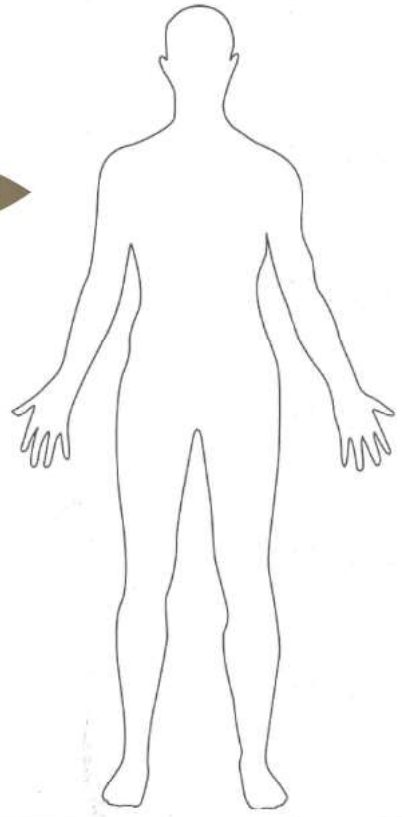
*(when [A] = [B])

Ref: http://www.chem.purdue.edu/gchelp/howtosolveit/Kinetics/Halflife.html#0Order

Toxicokinetics - modeling

Toxicokinetics

- description of the behaviour and fate of the toxicant in the body.

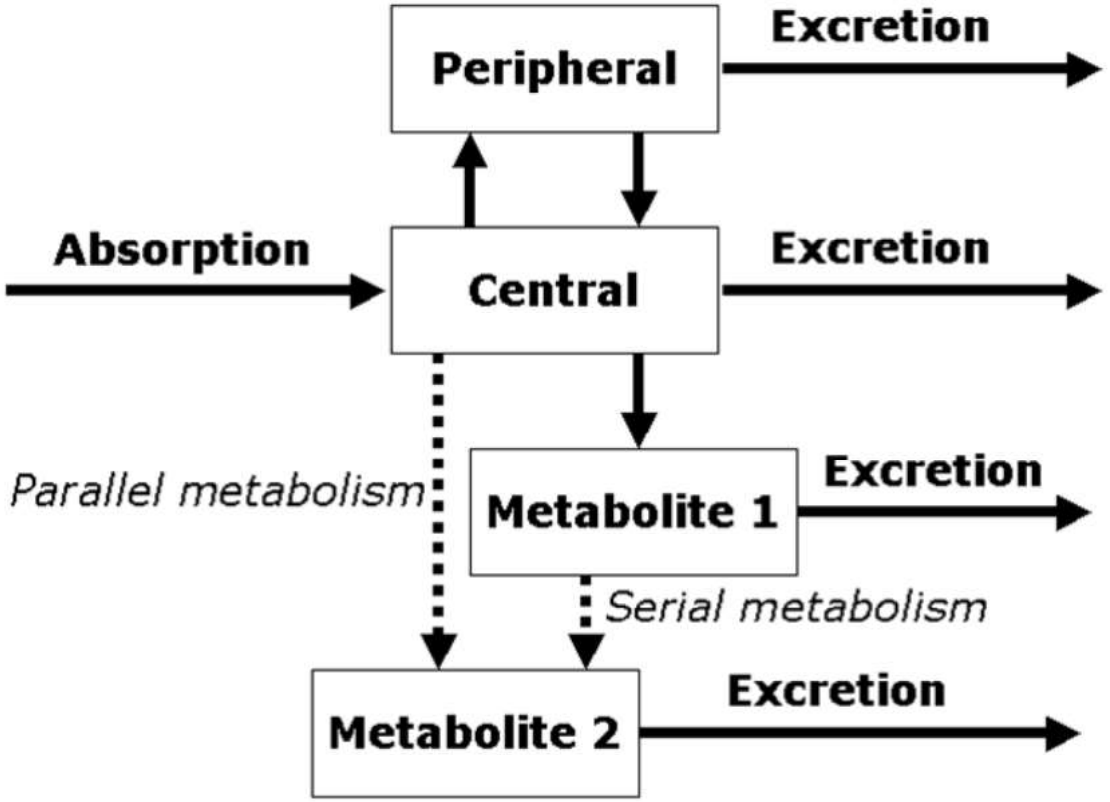
Exposure →  → Effect

- PBPK model, mathematical modeling (anatomical, physiological, physical, chemical) of the ADME process

Toxicokinetics - modeling

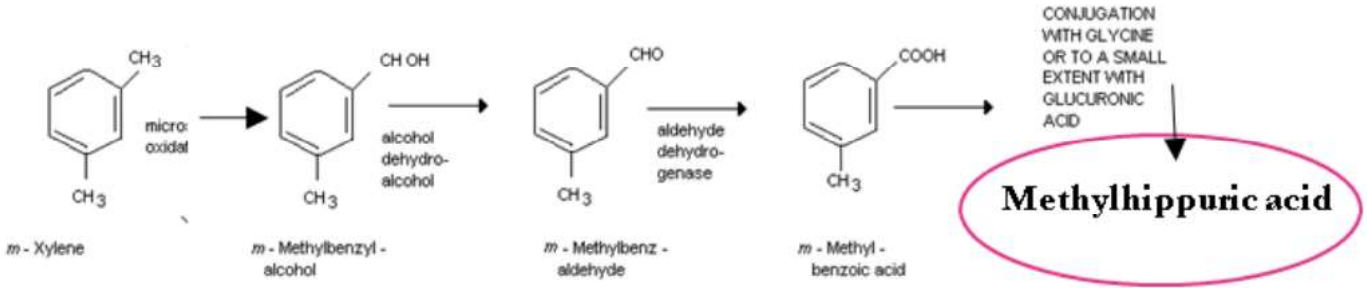
Toxicokinetics

- Model TK with compartments

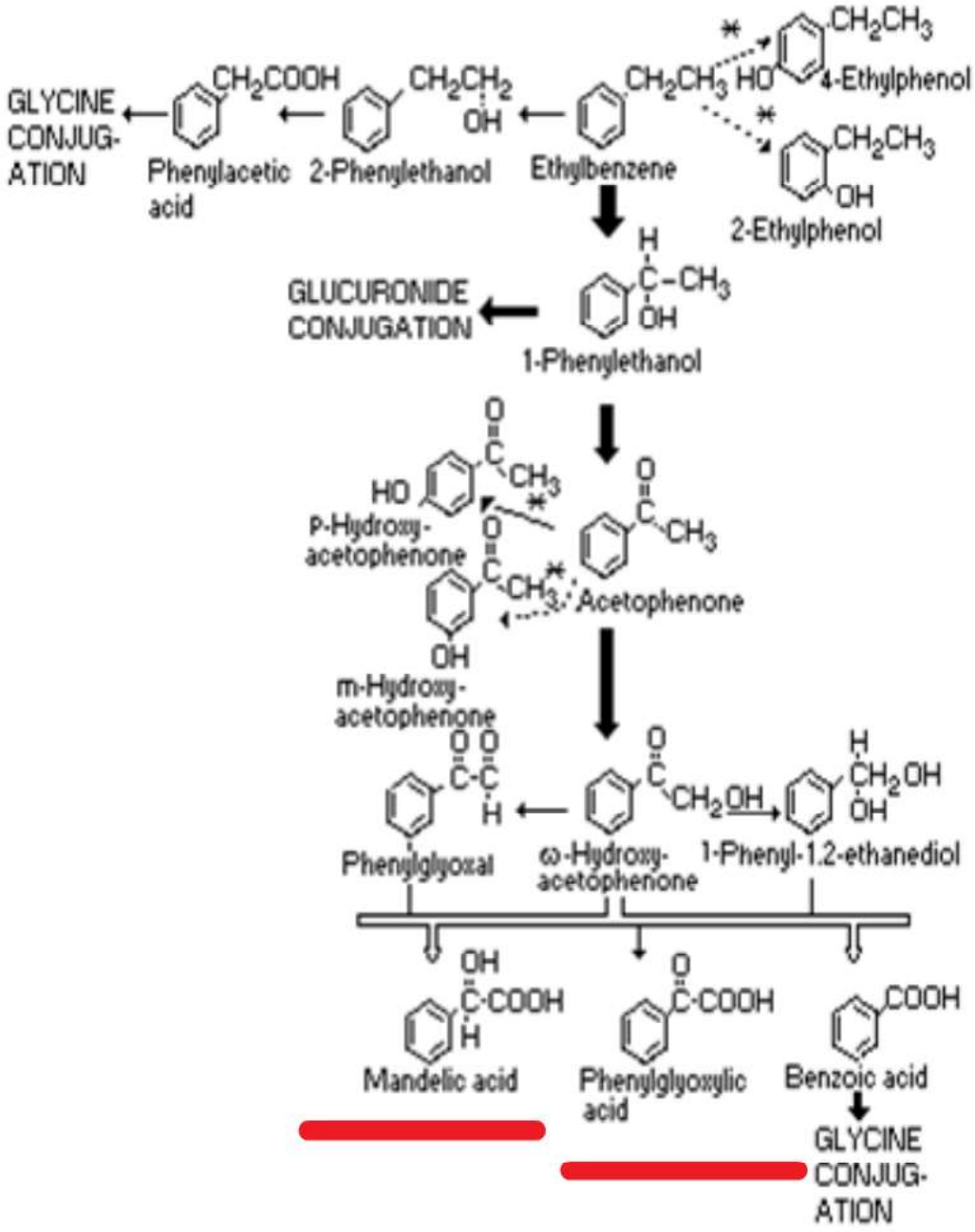


Toxicokinetics - modeling

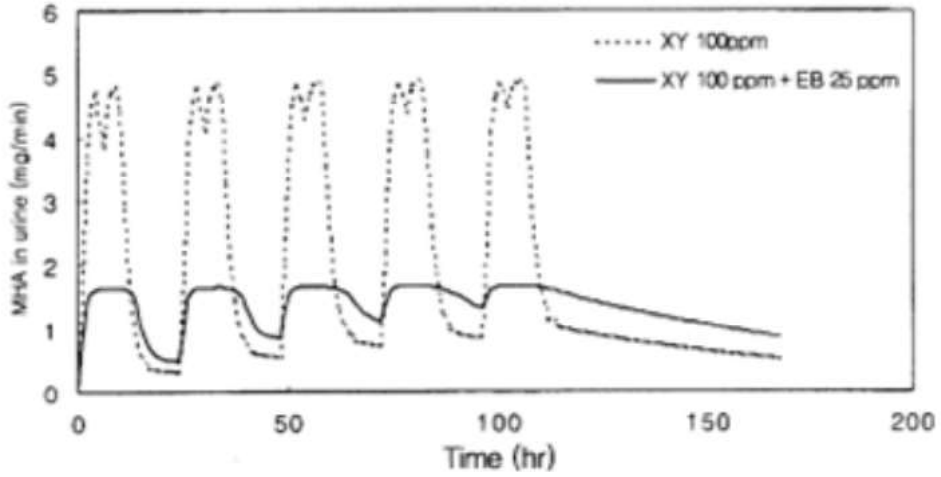
- Exposure to xylene and ethylbenzene in the metal industry
- effects of the two similar solvents (CNS)
- interference when co-exposed to both solvents

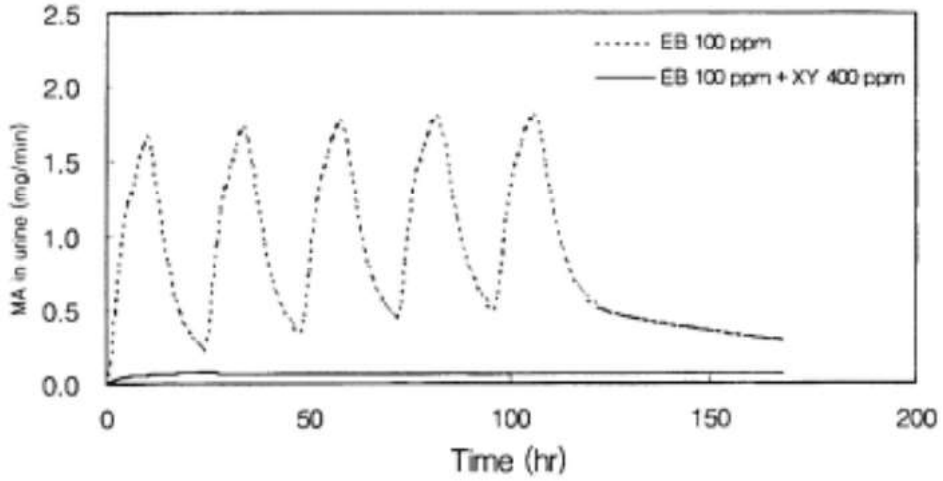


Toxicokinetics - modeling



Toxicokinetics - modeling





- Strong interaction between metabolic pathways
- EB metabolism strongly decreased by co-exposure
- MHA reduced 3x
- MA reduced 30x

Biomonitoring

Internal Dose Indicators

- Unchanged substance (metal, solvent) in blood, urine, exhaled air
- Metabolites (organic compounds) in blood, urine, saliva
- Biological determinant adducted to DNA or hemoglobin

Interest of biomonitoring

Takes into account
- physical effort
- all routes of penetration (skin absorption,ingestion, inhalation)
- personal protection
- fluctuations of the environment
- constitution: fat, muscle...
- metabolic differences

Biomonitoring

Disadvantages

- high intra/inter individual variability
- possible interference (alcohol, medication...)
- sometimes invasive
- does not detect exposure peaks
- limited to a few substances
- sometimes difficult to interpret

Reference values

- BEI (biological exposure indicies) in the USA
- BAT (biologischer arbeitsstoff-toleranz wert) in Germany

Biomonitoring strategy

Important factors

- Half-life of the biological indicator (metabolite)
- Exposure level
- Exposure variability
- Individual variability (diuresis /creatinine), renal function
- Timing of sampling

Biomonitoring strategy

Determinant	Media	T1/2 [h]	Timing
METALS			
Lead	blood	900	not critical
Chromium	urine	7	end of shift
Cadmium	urine	20 years	not critical
Nickel	urine	24	end of shift
SOLVENTS METABOLITES			
N-Methlyformamide	urine	4	end of shift
2,5-Hexadione	urine	15	end of shift
Trichloroethanol	blood	12	end of shift
Trichloroacetic acid	urine	80	end of shift at end of week
SOLVENTS			
Styrene	blood	0.5-4	end of shift
	blood	70	next morning
Methyl Ethyl ketone	urine	4	end of shift
Perchloroethylene	exhaled air/blood	96	prior to last shift of workweek

bloo

Assessment of toxicity

Structural analogy

- similar biological and chemical structures can produce similar responses (QSAR)

In-vitro evaluation

- mutagenicity test (Ames)
- cell culture (target organs)
- human and animal tissues

Animal experimentation

- acute and chronic tests in rats, mice and dogs
- choice of animal based on similarities to humans (aborption, metabolism)
- importance of route of entry

Human epidemiological data

- descriptive (disease prevalence), retrospective (exposure to a particular substance), prospective (risk assessment)
- health effects measured in exposed populations

Toxicological file

Minimum required according to REACH

Study type	study duration (months, ca.) 1	2	3	4	5	6	7	8	9	>9
Production volume > 1 t/a, Annex VII										
Skin irritation or corrosion in vitro										
Eye irritation in vitro										
Skin sensitization										
Mutagenicity: in vitro gene mutation study in bacteria										
Acute toxicity by oral route										

Study type	study duration (months, ca.) 1	2	3	4	5	6	7	8	9	>9
Production volume > 10 t/a, Annex VIII										
Skin irritation in vivo										
Eye irritation in vivo										
Mutagenicity: in vitro cytogenetic study in mammalian cells or in vitro micronucleus test										
Mutagenicity: in vitro gene mutation study in mammalian cells										
Acute toxicity by inhalation or by dermal route										
Repeated dose toxicity: 28 days (**most appropriate route of administration**)										
Reproduction toxicity: Screening test										

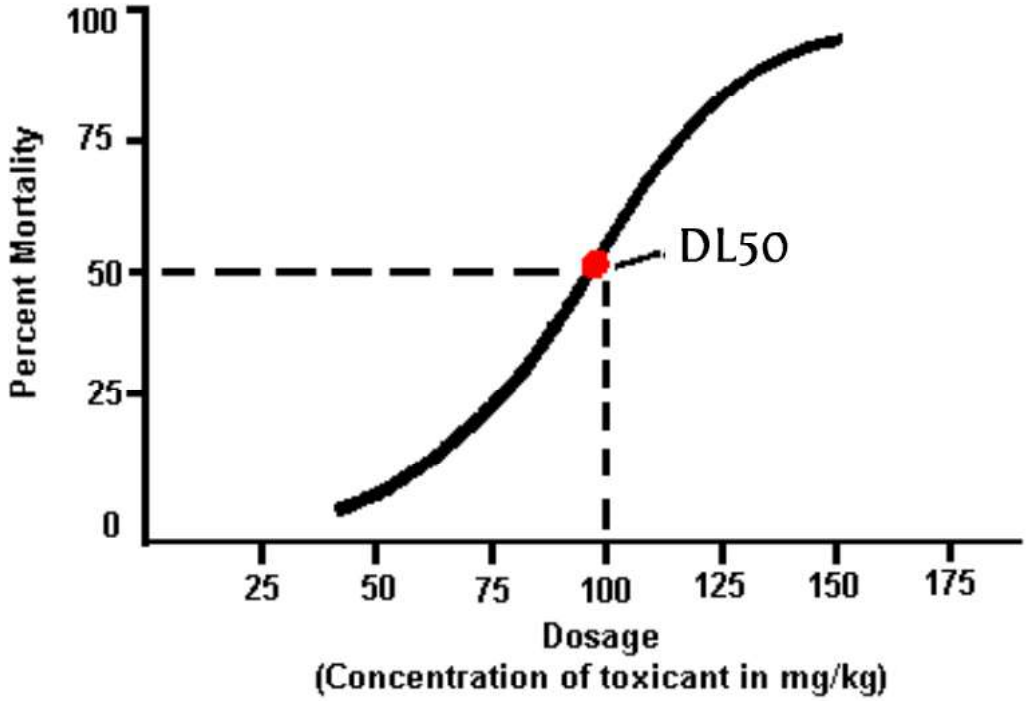
Toxicological file

Minimum required according to REACH

Study type	study duration (months, ca.)									
	1	2	3	4	5	6	7	8	9	>9
Production volume > 1000 t/a, Annex X										
Mutagenicity: second in vivo somatic cell genotoxicity study										
Repeated dose toxicity: ≥ 12 months										
Specific toxicological studies (neurotoxicity, immunotoxicity etc.)										
Further reproduction toxicity studies										
Carcinogenicity study										

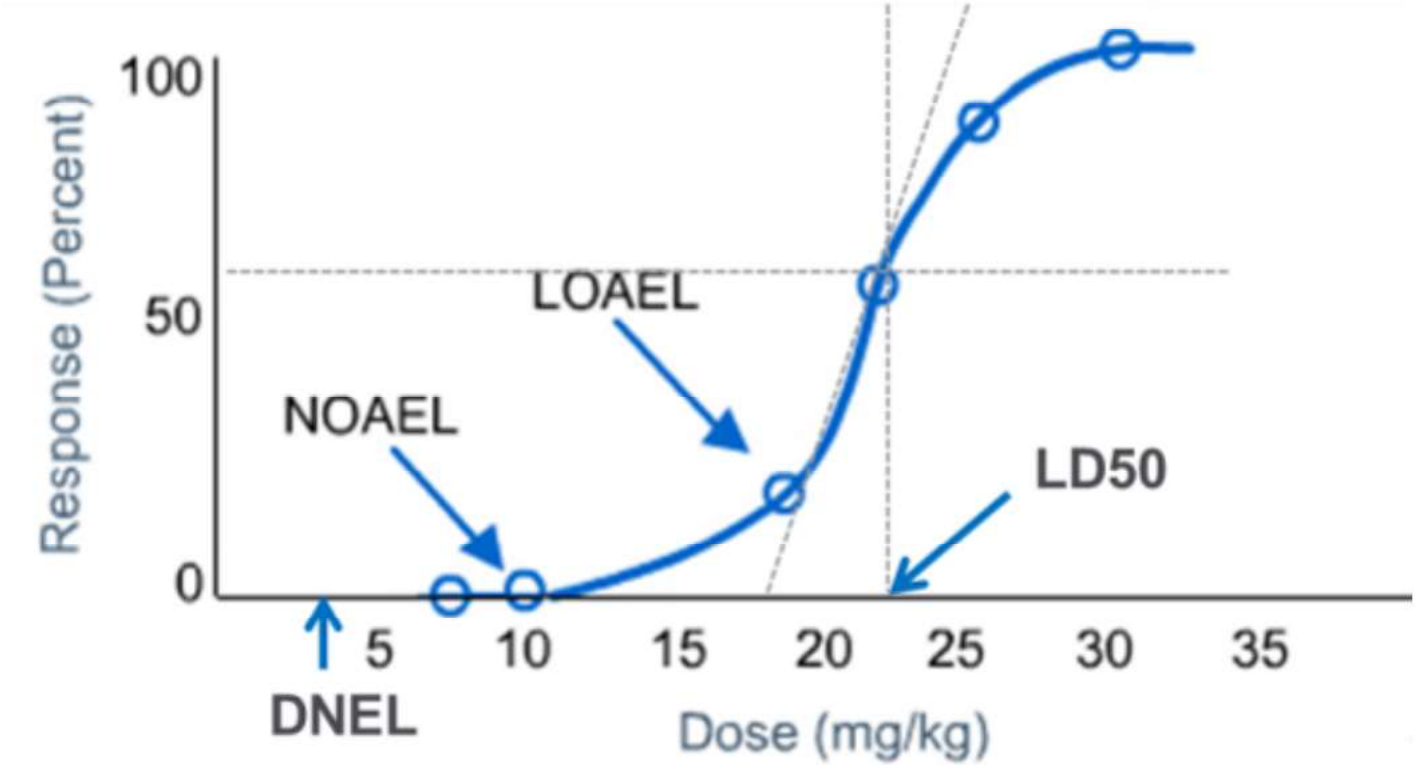
Dose-response relationship

classic relationship



NOAEL - No Observed Adverse Effect Level

Value assumed to have no effect



Limit values of exposure

TWA (VME: Valeur limite Moyenne d'Exposition)

Average concentration in the air of workstations of a given pollutant which, according to current knowledge, does not endanger the health of the vast majority of healthy workers exposed to it, for a duration of 42 hours per week, at a rate of 8 hours per day, for long periods

Short term TWA (VLE: Valeur limite d'Exposition)

- calculated over a short period of time
- limitation of intensity, time and frequency for exceeding the TWA
- average over 15 minutes
- delay between the 4 peaks minimum one hour..

VBT (tolerable biological values)
Physical agents
Physical constraints

Valeurs limites d'exposition aux postes de travail

suva

Elaboration of reference values

Instances

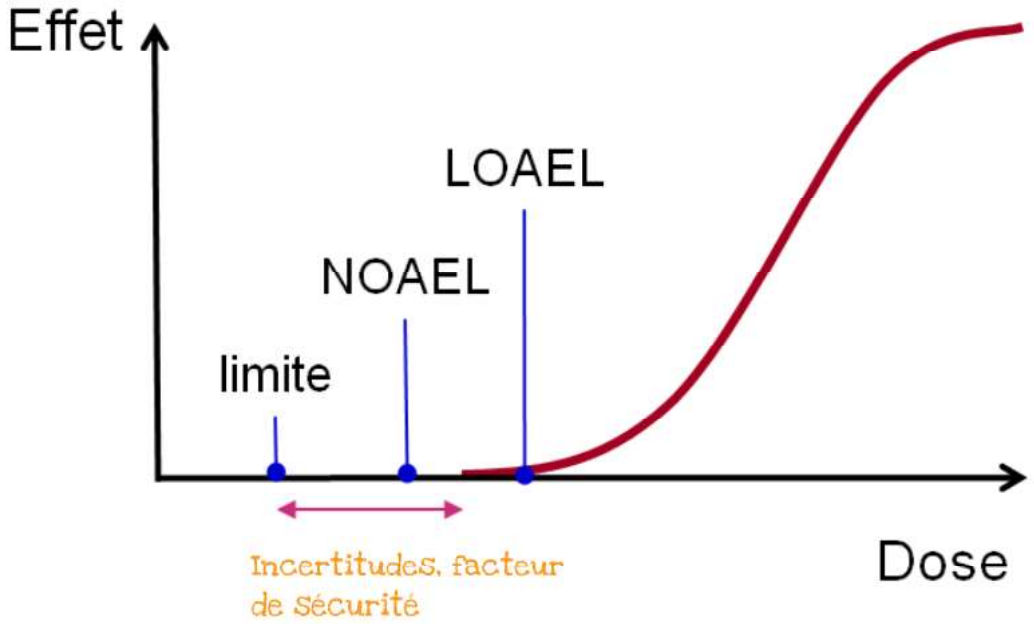
The Scientific Committee on Occupational Exposure Limits (SCOEL)

- Indicative OEL Values (IOELVs), n=160
- Binding OEL Values (BOELVs), n=10
- Skin notation, biological limit values (BLV)

National committees, in Switzerland the MAK commission

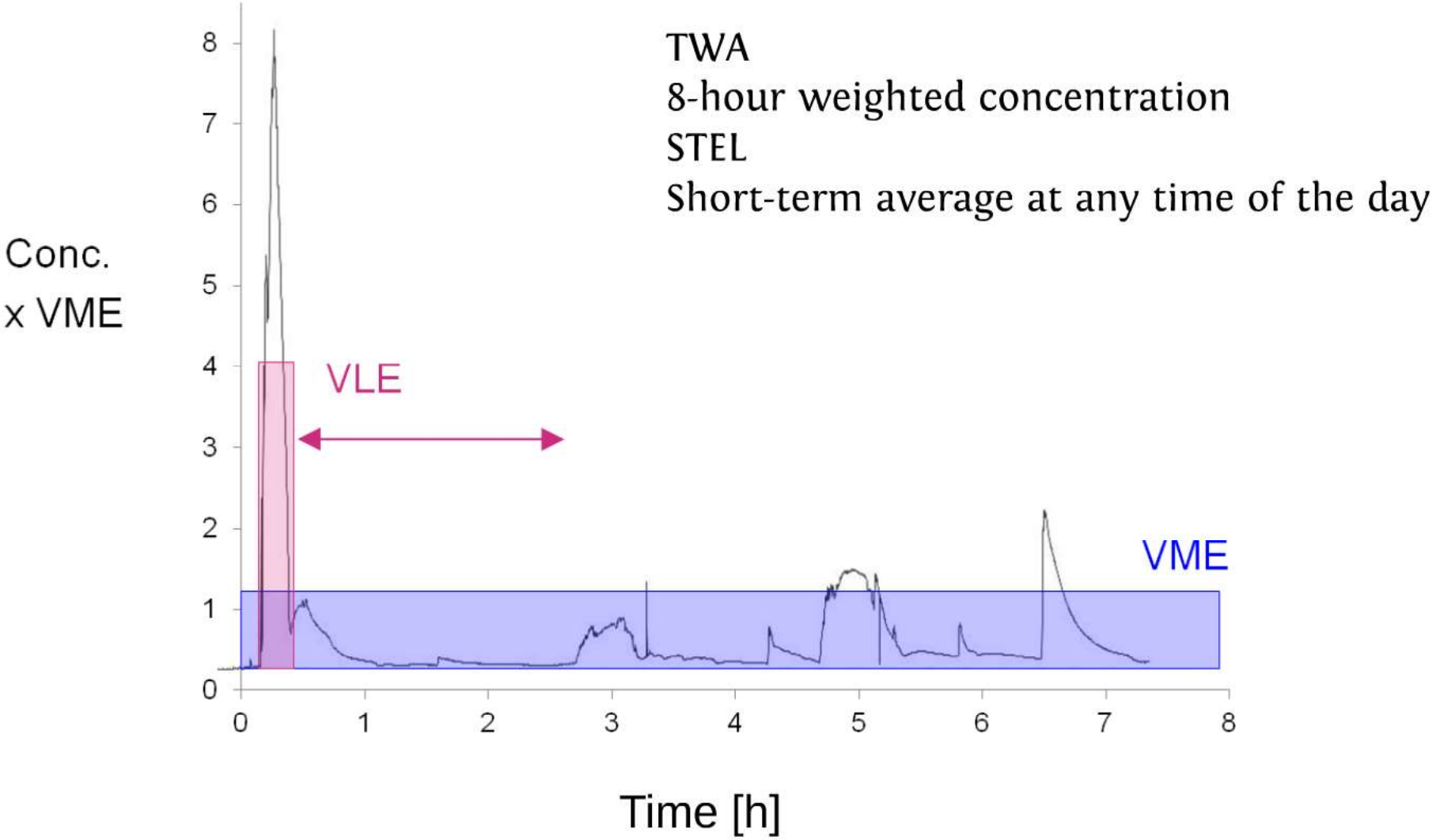
Approach

- Prioritization of substances
- Data analysis
- Critical effect
- POD point of departure (e.g. NOAEL)
- Assignment of uncertainty factors



Use of limit values (TWA)

TWA
8-hour weighted concentration
STEL
Short-term average at any time of the day



VME / VLE

Substance [no CAS]	VME		VLE		Notations	Toxicité critique	Indications analytiques/ Remarques
	ml/m³ (ppm)	mg/m³	ml/m³ (ppm)	mg/m³	R S O[B] B P C M R_F R_D SS		
Composés de Tétra-n-octylétain [7440-31-5] (exprimé en Sn)	0,004	0,02 i	0,004#	0,02 i#	R	Yeux, VRS, SNC, Nausée, Immun[TC AN]	
Ethane [74-84-0]	10000	12500				Arh, SNC, Formel[TC]	
Ethanol [64-17-5]	500	960	1000	1920	SS_C	VRS, Formel[TC HU]	INRS, NIOSH
Ethanolamine v. 2-Aminoéthanol							
Ether de bis(chlorométhyle) v. Oxyde de bis(chlorométhyle)							
Ether bis-2-méthoxypropylique v. Oxyde de dipropylèneglycolméthyle							
Ether 1-chloro-2,2,2-trifluoréthyl-difluorométhylique [26675-46-7]	10	77	80	616			
Ether 2-chloro-1,1,2-trifluoréthyl-difluorométhylique [13838-16-9]	10	77	80	616	SS_C		OSHA
Ether de pétrole 30–75 sans hydrocarbures aromatiques	500	2000				SNC, VRS[TC] & Yeux[TC]	OSHA Respecter la VME du n-Hexane
Ether α,α-dichlorodiméthylique v. Oxyde de bischlorométhyle							
Ether 2,2' dichlorodiéthylique [111-44-4]	5	30	5#	30#	R C_3	Yeux, Nausée, VR[TC]	NIOSH
Ether diisopropylique [108-20-3]	200	850	400	1700	SS_C	Yeux, VRS, Foie, Rein, Halitose[TC HU]	NIOSH
Ether diméthylique [115-10-6]	1000	1910				Formel[TC]	
Ether diméthylique du diéthylèneglycol [111-96-6]	5	27	40	216	R R_{F3}* R_{D3}* SS_B	ReproM & P[TC AN]	

VME / VLE

Substance	Paramètre biologique	VBT	Substrat d'examen	Prélèvement	Remarques
2-Ethoxyéthanol	Acide éthoxyacétique	50 mg/l (480,3 µmol/l)	U	c, b	
2-Ethoxyéthylacétate	Acide éthoxyacétique	50 mg/l (480,3 µmol/l)	U	c, b	
Ethylbenzène	Ethylbenzène	1,5 mg/l (14,1 µmol/l)	B	b	
	Acide mandélique + acide phénylglyoxylique	2 g/g créatinine	U	b	
Composés fluorés inorganiques et acide fluorhydrique	Fluorures	7 mg/g créatinine (41,6 nmol/mmol créatinine)	U	b	X
	Fluorures	4 mg/g créatinine (23,87 nmol/mmol créatinine)	U	d	X
Halotane	Acide trifluoroacétique	2,5 mg/l (12,6 µmol/l)	S	c, b	
Hexachlorobenzène	Hexachlorobenzène	150 µg/l (52,7 µmol/l)	P/Se	a	X
n-Hexane	2,5-Hexanedione + 4,5-Dihydroxy-2-hexanone	5 mg/l	U	b	N
2-Hexanone	2,5-Hexanedione + 4,5-Dihydroxy-2-hexanone	5 mg/l	U	b	N
Isopropanol	Acétone	25 mg/l (0,4 mmol/l)	U	b	
	Acétone	25 mg/l (0,4 mmol/l)	S	b	
Isopropylbenzène (Cumène)	2-Phényl-2-propanol	50 mg/g créatinine (41,5 µmol/mmol créatinine)	U	b	
Lindane (γ-1,2,3,4,5,6-Hexachlorocyclohexane)	Lindane	25 µg/l (85,9 nmol/l)	P/Se	b	
Manganèse et ses composés inorganiques	Manganèse	20 µg/l (364 nmol/l)	S	c, b	Q

Regulatory values, what they don't say

Substances without exposure limits

- Known substances 20'000'000
- Industrial substances 15'000
- Exposure limit values (TWA) 620
- Tolerable biological values (BTV) 45

Other limitations

- almost all workers
- hypersensitivity below the threshold
- existence of a residual risk in absence of threshold (carcinogens)
- limitations to healthy workers, limited age range
- cumulative exposure
- new knowledge